

CLAIMS:

1. An isolated nucleic acid molecule comprising a sequence of nucleotides or complementary sequence of nucleotides which encodes an amino acid sequence which is capable of signalling, inducing or otherwise facilitating the death of a cell in which said amino acid sequence is adjacent, proximal or otherwise juxtaposed to the membrane of said cell or when said amino acid is in multimeric form.
2. An isolated nucleic acid molecule according to claim 1 wherein the amino acid sequence comprises a membrane-associating portion and/or multimer-forming portion and a portion which corresponds to all or part of the cytoplasmic region of p75^{NTR} or a functional equivalent, derivative or homologue thereof.
3. An isolated nucleic acid molecule according to claim 2 wherein the membrane-associated portion is derived from p75^{NTR} or a functional equivalent, derivative or homologue thereof.
4. An isolated nucleic acid molecule according to claim 2 wherein the membrane-associating portion is from a receptor or other ligand-binding molecule.
5. An isolated nucleic acid molecule according to claim 4 wherein the receptor or other ligand-binding molecule is a cytokine receptor, immunoglobulin or T-cell receptor.
6. A homologue, analogue or derivative of the nucleic acid molecule of any one of claims 1 to 5.
7. An isolated nucleic acid molecule comprising a sequence of nucleotides which encodes an amino acid sequence which inhibits or reduces p75^{NTR}-mediated cell death wherein said amino acid sequence is a soluble form of the p75^{NTR} receptor corresponding to an intracellular region adjacent, proximal or otherwise

8. An isolated nucleic acid molecule according to claim 7 wherein the p75^{NTR} is of human, primate or murine origin.

10. An isolated nucleic acid molecule according to claim 9 comprising a nucleotide sequence substantially as set forth in <400>7 or a nucleotide sequence capable of hybridizing to <400>7 or its complementary form under low stringency conditions or a nucleotide sequence having at least 60% identity to <400>7.

Sub B15 12. A nucleic acid molecule comprising the nucleotide sequence:

$$\{n_1 - \dots - n_x\}_b a \{n'_1 - \dots - n'_y\}_c a \{n''_1 - \dots - n''_z\}_d$$

$\{n_1, \dots, n_x\}$ is a sequence of x nucleotides encoding an extracellular portion of a receptor or ligand-binding molecule;

~~{n₁ - - - n_z} is a sequence of z nucleotides comprising a nucleotide sequence substantially as set forth in <400>7 or a nucleotide sequence encoding an amino acid sequence substantially as set forth in <400>8 or a~~

Sub B15

nucleotide sequence capable of hybridising to <400>7 or a complementary form thereof under low stringency conditions such as at 42 °C or a nucleotide sequence having at least 60% identity to <400>7;

b, c and d may be the same or different and each is 0, 1 or >1;

x, y and z may be the same or different and each is 0, 1 or >1;

a is a nucleotide bond;

wherein when c is 1 or >1 and d is 1 or >1 and wherein when the molecule is expressed in a neural cell, the expression product signals, induces or otherwise facilitates cell death.

13. A nucleic acid molecule according to claim 12 wherein $\{n_1 - \dots - n_x\}$ comprises the nucleotide sequence substantially as set forth in <400>3 or is a nucleotide sequence having at least about 60% identity thereto or is capable of hybridising thereto under low stringency conditions at 42°C.

14. A nucleic acid molecule according to claim 12 wherein $\{n'_1 - \dots - n'_y\}$ comprises the nucleotide sequence substantially as set forth in <400>5 or is a nucleotide sequence having at least about 60% identity thereto or is capable of hybridising thereto under low stringency conditions at 42°C.

15. A genetic construct comprising an isolated nucleic acid molecule which comprises a sequence of nucleotides which corresponds or is complementary to a death signal region from p75^{NTR} or a homologue, analogue or derivative thereof.

16. A genetic construct according to claim 15 wherein the coding region of the death signal from p75^{NTR} is placed in operable connection with a promoter sequence such that a gene product is capable of being expressed under the control

of said promoter sequence.

17. A genetic construct according to claim 15 or 16 wherein said genetic construct further comprises a terminator sequence.

18. A method for inhibiting, reducing or otherwise antagonising p75^{NTR}-mediated death signal in a neural cell, said method comprising administering a peptide, polypeptide or protein or analogues or mimetics thereof which correspond to a non-membrane associated form of the p75^{NTR} death signal region or a derivative, functional equivalent or homologue thereof.

19. A peptide antagonist of the p75^{NTR} death signal or functional analogues or mimetics thereof.

20. A recombinant peptide, polypeptide or protein produced by expressing the isolated nucleic acid molecule according to any one of claims 1 to 14 in a suitable host cell or a derivative, homologue or analogue of said peptide, polypeptide or protein.

21. An isolated peptide, polypeptide or protein according to claim 20 comprising the cytoplasmic region of p75^{NTR} which signals, induces or otherwise facilitates cell death when said peptide, polypeptide or protein is adjacent, proximal or otherwise juxtaposed to a membrane-associating region such as from p75^{NTR} or other membrane molecule and/or is in multimeric form or a derivative, homologue, chemical equivalent or analogue of said peptide, polypeptide or protein.

22. A peptide, polypeptide or protein according to claim 21 comprising an amino acid sequence substantially as set forth in <400>8 or an amino acid sequence having at least 60% identity thereto or a chemical equivalent, derivative, homologue or analogue of said peptide, polypeptide or protein.

23. A method for inhibiting, reducing or otherwise antagonising a p75^{NTR}-mediated death signal in a neural cell, said method comprising introducing a nucleic acid molecule capable of being expressed to an expression product which corresponds to a non-membrane associated form of the p75^{NTR} death signal region or a derivative, functional equivalent or homologue thereof.

24. A method for inhibiting, reducing or otherwise antagonising a p75^{NTR}-mediated death signal in a neural cell, said method comprising contacting a cell carrying a p75^{NTR} with a death signal-inhibiting effective amount of a molecule capable of antagonising the death signal of p75^{NTR} or a component of the death signalling pathway.

25. A method according to claim 23 or 24 for the treatment of a range of neurodegenerative diseases such as cerebral palsy, trauma induced paralysis, vascular ischaemia associated with stroke, neural tumours, motoneurone disease, Parkinson's disease, Huntington's disease, Alzheimer's disease, multiple sclerosis and peripheral neuropathies associated with diabetes, heavy metal or alcohol toxicity, renal failure and/or infectious diseases such as herpes, rubella, measles, chicken pox, HIV and/or HTLV-1.

26. A method according to claim 23 or 24 for treating neurons and neural cells damaged by trauma or disease.

27. A biological composition comprising a genetic molecule capable of being expressed into a p75^{NTR} death signal antagonist or a p75^{NTR} death signal said composition further comprising one or more pharmaceutically acceptable carriers and/or diluents.

28. A method for modulating p75^{NTR}-mediated death signal in a neural cell, said method comprising administering an agent which antagonises or agonises cleavage of the extracellular domain of p75^{NTR}.

29. Use of an antagonist of the death signal of p75^{NTR} in the manufacture of a medicament for the treatment of neurodegenerative diseases in animals.

30. Use according to claim 29 wherein the animal is a human, primate, livestock animal, laboratory test animal, companion animal and/or captive wild animal.

19
-53-